

Case-Control Study of Childhood Acute Lymphoblastic Leukemia and Residential Radon Exposure

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Background: Several ecologic analyses have shown significant positive associations between mean indoor radon concentrations and risk of leukemia at all ages (acute myeloid leukemia and chronic lymphocytic leukemia) and for children (all leukemia, acute myeloid leukemia, and acute lymphoblastic leukemia [ALL]). As part of an age-matched, case-control study of childhood ALL in the United States, we investigated the association between the incidence of ALL in children under age 15 years and indoor radon exposure. **Methods:** Radon detectors were placed in current and previous homes of subjects where they resided for 6 months or longer. Children were included in analyses if radon measurements covered 70% or more of the 5-year period prior to diagnosis for case subjects (or from birth for case subjects under age 5 years) and the corresponding reference dates for control subjects. Radon levels could be estimated for 97% of the exposure period for the eligible 505 case subjects and 443 control subjects. **Results:** Mean radon concentration was lower for case subjects (65.4 becquerels per cubic meter [Bqm^{-3}]) than for control subjects (79.1 Bqm^{-3}). For categories less than 37, 37–73, 74–147, and 148 or more Bqm^{-3} of radon exposure, relative risks based on matched case-control pairs were 1.00, 1.22, 0.82, and 1.02, respectively, and were similar to results from an unmatched analysis. There was no association between ALL and radon exposure within

subgroups defined by categories of age, income, birth order, birth weight, sex, type of residence, magnetic field exposure, parental age at the subject's birth, parental occupation, or parental smoking habits. **Conclusions:** In contrast to prior ecologic studies, the results from this analytic study provide no evidence for an association between indoor radon exposure and childhood ALL. [J Natl Cancer Inst 1998;90:294–300]

Inhalation of high cumulative levels of radioactive radon gas (radon-222) and, in particular, its α -particle-emitting decay products has been linked to an increased risk of lung cancer among underground miners (1). Exposure to lower levels of residential radon has also been tied to lung cancer in some but

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not all studies of radon in homes (2). While highly exposed miners have not been observed to develop cancers at any anatomic site other than lung (3), concern has developed about possible associations of indoor radon exposure with other cancers; this concern follows publication of ecologic analyses showing significant positive correlations between county radon level in the U.K. and incidence of acute myeloid leukemia for all ages (4) and mortality from acute lymphoblastic leukemia (ALL) in children (5). Mean radon levels in 15 countries were significantly correlated with incidence rates for all childhood cancers and, specifically, for all leukemias, brain cancer, osteosarcoma, and melanoma and for all adult leukemias, although not for lung cancer (6). These reports were met with considerable criticism (7–13), including more refined ecologic analyses that failed to confirm the initial associations (14,15). The only case-control study to date (16) found no association between the occurrence of childhood cancer and indoor radon exposure; however, that study included only 15 case subjects and 15 control subjects. Nonetheless, dosimetric calculations suggest that inhaled radon might impart a radiation dose to red bone marrow and to anatomic sites other than the lung (17–21).

As part of a large comprehensive case-control study in the United States of childhood ALL (22), we measured radon in current and previous homes of study subjects to investigate the association between childhood ALL and exposure to radon and its progeny.

Subjects and Methods

For the main study, case subjects were eligible if aged under 15 years at diagnosis, diagnosed with ALL during the period 1989–1993, and treated by physicians affiliated with the Children's Cancer Group (CCG) throughout the United States (22,23).

Control subjects were selected by random-digit dialing. They were individually matched to case subjects on age (within 3 months for case subjects aged under 1 year, within 25% of the age at diagnosis for case subjects aged 1–8 years, and within 2 years for case subjects aged 8 years and over) at diagnosis, race, and the first eight digits of the telephone number.

For the radon study, case subjects and control subjects were required to have resided in one of nine Midwestern or mid-Atlantic states (Illinois, Indiana, Iowa, Michigan, Minnesota, New Jersey, Ohio, Pennsylvania, and Wisconsin) at the reference date (date of ALL diagnosis for the case subject or the corresponding date for the matched control subject). A total of 900 (96%) of 942 eligible case subjects and 973 (75%) of 1292 eligible control subjects were enrolled in the CCG study. Among these subjects, 767 case subjects and 725 control subjects met the eligibility criteria for the magnetic field measurement component of the study, while 638 (83%) case subjects and 620 (86%) control subjects agreed to participate (23). Within each state listed above, case subjects and control subjects totaled 60 and 58, 40 and 39, 47 and 52, 89 and 83, 78 and 73, 69 and 62, 123 and 117, 127 and 129, and 5 and 7, respectively. We excluded nine case subjects and one control subject with Down syndrome because patients with this disorder are at a 10-fold to 40-fold increased risk of developing ALL (24).

Information on demographic, socioeconomic, and other factors was obtained through a comprehensive telephone interview of mothers and fathers. This interview was conducted for the main study. A second telephone interview obtained information on residential history, which was used to assess eligibility for the magnetic field and radon components of the study and schedule an in-person interview.

Radon Measurements and Exposure Assessment

Subjects qualified for the radon study if their residential histories satisfied the requirements of the magnetic field measurement protocol (22). Since there has been no previous study relating α radiation from indoor radon to ALL in chil-

dren, the appropriate radon exposure period for a possible association with childhood ALL is unknown. A 5-year interval would be sufficient if α radiation emitted from radon and radon decay products had similar effects as γ and x irradiation. The protocol for the measurement of indoor radon paralleled the protocol for measurement of magnetic fields, which was the motivation for the current study. For children under age 5 years, efforts were made to measure all homes in which the subject resided for 6 months or longer. Subjects were included provided that the measured homes covered at least 70% of the child's life. For children aged 5 years and older, homes in which the subject resided for 1 year or longer within the 5-year period prior to the reference date were measured. Subjects were included provided that no more than two measured homes covered at least 70% of the child's life during the period. The minimum residency criterion for each measured house represented about 20% of the exposure period of interest (6 months for children aged 2.5 years, the midpoint of the age interval 0–5 years, and 1 year for the 5-year interval for children older than 5 years).

Two track-etch radon detectors (TechOps-Landauer, Glenwood, IL) were placed for 1 year in each qualifying residence. One detector was placed in the child's bedroom, and the other was placed in the family room; we used standard placement procedures as recommended by the U.S. Environmental Protection Agency. Rooms above the third floor were not measured but were assumed to contain ambient radon levels. For children under age 5 years and for current and previous houses, an additional radon detector was placed in the mother's bedroom if she slept in the room at least 5 months while the child was *in utero*. Every 4 months, homeowners were contacted to verify that the detectors remained in place. After 1 year, detectors were placed in sealed pouches by the homeowners and returned by mail to TechOps-Landauer for evaluation. To ensure measurement quality, duplicate detectors were placed in 10% of the homes and detectors exposed at known radon concentrations were sent for evaluation.

Detectors measured radon in becquerels per cubic meter (Bq m^{-3}). A historical unit, still in use, is the pico-curie per liter (pCi L^{-1}) for which 1 pCi L^{-1} equals 37 Bq m^{-3} . In response to concerns about lung cancer risk from indoor radon, the U.S. Environmental Protection Agency recommends remediation of homes with concentrations above 148 Bq m^{-3} (4 pCi L^{-1}).

As a measure of exposure, we computed time weighted average (TWA) radon concentration within the exposure assessment period for each subject; lengths of residence served as weights. For children under age 5 years, TWA radon level was the weighted concentration in homes from birth through age at the reference date. For children aged 5 years and older, TWA radon level was the weighted concentration in homes occupied in the 5-year period before the reference date. For each home, radon level was the mean of all detectors, weighted by an estimate of time a child spends in each room (25,26).

Radon measurements were not always available for a home because of refusal by the subject or current occupant of the subject's former home, location outside the study areas, or other reasons. Missing exposure times (up to 30% of the exposure period for subjects in the radon analysis) were imputed with the use of mean radon level in all control homes. This imputation approach was contrasted with two alternative methods. In the first method, we used mean radon concentration of all homes within the state to replace missing data. In the second method, we used the mean concentration within state and housing type (apartment, duplex, single-family house, row house, or townhouse, trailer or mobile home, and other) to replace missing measurements. Housing type was included to increase the predictive ability for estimating missing radon measurements, since housing configuration, e.g., type of ground contact (basement or crawlspace), and number of levels in a house are related to indoor radon concentration.

Because of the potentially rapid appearance of leukemia after radiation exposure (27), we computed TWA radon level for the entire exposure assessment period. Results were contrasted with TWA radon level computed by use of a 2-year lag interval; i.e., exposures within 2 years of the referent date are ignored.

Methods of Analysis

Relative risks (RRs), based on regression analysis for matched case-control studies (28), were used to estimate the association of ALL and residential radon concentration. Since control subjects were age matched to case subjects, the regression approach estimates RRs. We also estimated RRs, as approximated by odds ratios, using an unconditional logistic regression (28), stratifying on age at reference date and sex. Results from the matched and unmatched analyses were similar. The 95% confidence interval (CI) was computed by use of the standard

error of the category-specific log-RR parameter estimate. Tests for linear trend were based on a score test by use of the continuous value for the TWA radon level. All *P* values are two-sided.

Results

Five hundred eighty-nine (92% of 638) participating case subjects and 538 (87% of 620) participating control subjects had available residential radon data. A total of 505 (79% of 638) case subjects and 443 (71% of 620) control subjects fulfilled the 70% coverage requirement of the measurement protocol and served as the basis for the unmatched analyses. These 948 subjects resided in 1365 homes. We found 1277 eligible homes and measured radon in 1124 (88%) of them. Among subjects fulfilling the radon measurement protocol, we had a total of 281 individually matched case-control pairs.

Mean TWA radon concentrations were 65.4 Bqm^{-3} for case subjects and 79.1 Bqm^{-3} for control subjects in the matched data and 68.7 Bqm^{-3} for case subjects and 75.7 Bqm^{-3} for control subjects in the unmatched data. For less than 37, 37–73, 74–147, and 148 or more Bqm^{-3} (corresponding to <1, 1–1.9, 2–3.9, and $\geq 4 \text{ pCiL}^{-1}$), RRs (95% CIs) were 1.00, 1.22 (0.8–1.9), 0.82 (0.5–1.4), and 1.02 (0.5–2.0), respectively, indicating no association between radon exposure and ALL (*P* = .18 for test of trend) (Table 1). The cut points used here were similar to those used in other radon studies (1,2). Results were similar for the unmatched analysis, where sex- and age-adjusted category-specific RRs (95% CIs) were 1.00, 1.30 (0.9–1.8), 0.91 (0.6–1.3), and 1.44 (0.9–2.3), respectively (*P* = .33 for test of trend).

Table 2 shows RRs for radon levels within categories of several variables that may confound the association or may serve as surrogates for other risk variables, including age at reference date, total household income, birth order, birth weight, sex, type of residence, and TWA magnetic field measurement. In this table, each variable was assessed separately. There was no significant association between ALL and radon exposure within the level of any of the other factors. For several variables, the observed category-specific RRs appeared to increase, while the test for trend indicated a negative gradient. This was the result of the arbitrary choice of cut points defining the categories and our use

of the continuous radon level in the test for trend. In no instance did the use of category-specific mean radon concentration alter inference. We also found no association within subgroups defined by type of house of longest residence, maternal and paternal ages at the subject's birth, and parental occupations and smoking habits (not shown).

In the matched data, 381 (67.8%) of 562 children (281 case-control pairs) lived in only one home and 513 (91.3%) lived in one or two homes. Table 3 shows no significant RR trends when data were restricted to children who lived in only one home or two or fewer homes during the exposure assessment period. For both case subjects and control subjects, 97% of the exposure period was covered by radon measurements. There was no significant association when data were restricted to children with more complete coverage of the exposure time period, and results were not affected by the method of imputing missing measurement data (Table 3).

Finally, there were no associations between ALL and TWA radon level computed by use of a 2-year lag interval or use of the radon level measured in the bedroom of the subject's mother while the child was *in utero* (Table 3).

Discussion

The hypothesis relating indoor radon exposure and childhood leukemia was based on results of ecologic studies, a procedure by which area disease rates are compared with area estimates of indoor radon levels. Ecologic studies (29–31) have recognized limitations that can seriously compromise their validity. For example, it is not known whether children diagnosed with leukemia in a specific region actually lived there for a meaningful period of time. Information on potential confounding variables may be unavailable, and there is no assurance that individual-level confounding is controlled through the inclusion of area-level variables (32). Surveys show that radon in homes in the same geographic area can vary by several orders of magnitude (33,34), potentially limiting the value of area means determined from relatively few measurements as estimates of exposure for all children in the same area.

Table 1. Number of case subjects and control subjects, relative risk (RR), and 95% confidence intervals (CI) for acute lymphoblastic leukemia by categories of time weighted average radon concentration within the exposure assessment period*

	Radon concentration, Bqm ⁻³				Total	P†
	<37	37–73	74–147	≥148		
<i>Matched analysis</i>						
No. of case subjects	116	90	48	27	281	
No. of control subjects	120	74	59	28	281	
Mean	20.1	53.7	97.4	300.7	72.3	
RR (95 CI)‡	1.00 (reference)	1.22 (0.8–1.9)	0.82 (0.5–1.4)	1.02 (0.5–2.0)		.18
<i>Unmatched analysis</i>						
No. of case subjects	202	160	84	59	505	
No. of control subjects	197	117	89	40	443	
Mean	19.7	53.6	98.3	286.6	71.9	
RR (95% CI)‡,§	1.00 (reference)	1.30 (0.9–1.8)	0.91 (0.6–1.3)	1.44 (0.9–2.3)		.33

*For children under age 5 years, the exposure period was from birth to the referent date. For children aged 5 years and over, the exposure period was 5 years prior to referent date. The referent date was the date of diagnosis for the case subject or the corresponding date for the matched control subject.

†Two-sided *P* value for test of linear trend in RRs. Parentheses indicate negative trend.

‡All RRs are adjusted for sex.

§RRs are also adjusted for age.

Table 2. Numbers of case subjects and control subjects and relative risk (RR) for acute lymphoblastic leukemia by categories of time weighted average radon concentration within the exposure assessment period*

	No. of case subjects/No. of control subjects	RR by radon concentration, Bqm ⁻³ †				P‡
		<37	37–73	74–147	≥148	
Age at reference date, y						
<2	23/23	1.00	0.63	0.26	0.28	(.12)
2–4	130/130	1.00	1.43	1.12	1.43	(.28)
5–9	83/83	1.00	0.89	0.51	0.54	(.90)
≥10	45/45	1.00	1.22	1.31	1.36	(.91)
Total household income, ×1000§						
<\$20	68/50	1.00	1.96	2.06	0.68	(.29)
\$20–\$49	115/104	1.00	0.86	0.82	0.74	(.26)
≥\$50	91/120	1.00	1.94	0.75	2.45	(.82)
Birth order						
1	104/116§	1.00	0.80	0.56	0.78	(.28)
2	107/87	1.00	1.63	1.12	2.28	.22
≥3	69/77	1.00	1.09	0.46	0.47	(.21)
Birth weight, g						
<3260	90/91	1.00	1.45	1.27	1.11	(.87)
3260–3684	88/99	1.00	1.57	0.78	2.09	(.74)
≥3685	103/91	1.00	1.02	0.71	0.56	(.05)
Sex						
Male	139/152	1.00	1.09	0.66	1.10	(.27)
Female	142/129	1.00	1.36	0.98	0.73	(.44)
Type of house of longest residence						
Single family	243/248	1.00	1.48	0.97	1.07	(.85)
Other	38/33	1.00	0.65	0.39	∞	(.19)
Time weighted average magnetic field measurement, μT§,						
<0.65	120/128	1.00	1.14	0.70	0.96	(.20)
0.65–0.99	60/55	1.00	1.11	0.80	1.77	.85
1.0–1.99	58/67	1.00	1.48	0.68	0.64	(.48)
≥2.0	34/22	1.00	0.93	1.45	0.64	(.77)

*For children under age 5 years, the exposure period was from birth to the referent date. For children aged 5 years and over, the exposure period was 5 years prior to referent date. The referent date was the date of diagnosis for the case subject or the corresponding date for the matched control subject.

†RRs are based on a matched analysis and are adjusted for sex. Each factor is evaluated separately.

‡Two-sided *P* value for test of linear trend in RRs. Parentheses indicate negative trend.

§Number of pairs are 274, 280, and 272, respectively, because of missing values.

||μT = microtesla; time weighted average magnetic field exposure with use of time lived in the residence as weight. Within a home, magnetic field exposure was computed as $(0.431 \times B + 0.160 \times F + 0.035 \times K)/0.626$ for subjects under 9 years old and $(0.396 \times B + 0.083 \times F + 0.021 \times K)/0.500$ for subjects ≥9 years old, where *B*, *F*, and *K* are magnetic field measurements in the child's bedroom, family room, and kitchen, respectively. The weights reflect the relative lengths of time spent in each room.

Table 3. Numbers of case-control pairs and relative risk (RR) for acute lymphoblastic leukemia by categories of time weighted average radon concentration within the exposure assessment period*

Matched pairs†	RR by radon concentration, Bqm ⁻³ ‡				P§	Data adjustment
	<37	37–73	74–147	≥148		
217/155	1.00	1.50	0.77	1.00	(.07)	Subjects with ≥90% coverage of the exposure period
162/122	1.00	1.63	1.05	1.62	(.54)	Subjects with 100% coverage of the exposure period
135/106	1.00	1.38	0.79	1.36	(.23)	Subjects who lived in one house
236/167	1.00	1.08	0.68	0.98	(.15)	Subjects who lived in one or two houses
281/201	1.00	1.30	0.84	1.05	(.19)	Missing radon measurements imputed by use of mean radon level within state
281/201	1.00	1.30	0.85	1.06	(.19)	Missing radon measurements imputed by use of mean radon level within state and housing type
281/197	1.00	1.20	0.92	1.23	(.55)	Mean radon concentration computed with 2-y lag interval
115/80	1.00	0.87	0.90	1.00	(.12)	Mean radon concentration while <i>in utero</i>

*For children under age 5 years, the exposure period was from birth to the referent date. For children aged 5 years and over, the exposure period was 5 years prior to referent date. The referent date was the date of diagnosis for the case subject or the corresponding date for the matched control subject.

†The first entry is the total number of complete matched pairs; the second entry is the number of informative matched pairs with different radon values.

‡Computation of radon concentration was adjusted to evaluate various factors. RRs are based on a matched analysis and are adjusted for sex.

§Two-sided *P* value for test of linear trend in RRs. Parentheses indicate negative trend.

||Radon concentration while *in utero* estimated only for subjects under age 5 years at ascertainment. The number of matched pairs was limited because of measurement refusals by current residents.

Some ecologic studies have shown significant correlations between mean radon concentration and rates for acute myeloid leukemia (4), chronic lymphocytic leukemia (5), non-Hodgkin's lymphoma (5), Hodgkin's disease (5), and childhood ALL (5). For all ages, Henshaw (6) found significant correlations between radon level and rates of myeloid leukemia, kidney cancer, and malignant melanoma but no association between radon level and lung cancer rates. For childhood cancers, Henshaw (6) found significant correlations between radon level and rates of all cancers, leukemia, brain and central nervous system cancers, osteosarcoma, and melanoma, as well as rates of Wilms' tumor and soft tissue sarcomas, although *P* values (*P* = .10) for these latter two sites did not reach the traditional level of statistical significance. Many of these associations are inconsistent with previous radiation research. There is only weak evidence of associations between ionizing radiation exposure and kidney cancer and non-Hodgkin's lymphoma, and there is little or no evidence of an association between radiation exposure and chronic lymphocytic leukemia, Hodgkin's disease, or Wilms' tumor (35). There is also little evidence of an association between exposure to radiation (other than nonionizing UV radiation) and melanoma (20). In contrast, there is strong evidence for an association between radon exposure and lung cancer (1).

Data suggest that some of these ecologic studies of radon exposure and cancer may have been influenced by inaccurate cancer diagnoses (9) or confounded by socioeconomic factors (13). Muirhead et al. (36) used data from 459 county districts for 1969–1983 and noted that the positive association between indoor radon exposure and county rates of childhood leukemia reversed to a negative association when data were analyzed by districts within county, suggesting the presence of district level confounding.

There is evidence, however, that inhaled radon can deliver a small radiation dose to tissues other than lung tissue. Lead-210 (a long-lived decay product of radon-222) is osteotropic (37,38). Radon-exposed miners with lung cancer have significantly higher levels of externally measured, skeletal lead-210 than control subjects, although exposures were one to two orders of magnitude greater than indoor exposures (39). In peripheral lymphocytes, there was an increased frequency of cells containing dicentrics and ring chromosomes, and there was an increased incidence of dicentrics and ring chromosomes per cell in 25 subjects living in homes with high radon exposure (200–3000 Bqm⁻³) compared with control subjects (40), although a larger report by the same investigators (41) failed to confirm their initial report.

We found no association between radon exposure and ALL despite many children in our study living in homes with high radon levels. Radon concentrations ranged from 4 Bqm⁻³ to 2194 Bqm⁻³, and the mean concentration was 70 Bqm⁻³. This mean level was about 50% higher than the mean level for all U.S. homes (46.3 Bqm⁻³), although it was similar to the regional levels that included the nine states in the study (33). Dosimetric calculations suggest that long-term residence in a home at 40 Bqm⁻³ results in an α dose equivalent of 20–200 microsieverts per year (μ Svy⁻¹) to bone marrow, depending on the relative biologic effectiveness assumed for α particles (18,19,21). Thus, 300 Bqm⁻³ (the mean in the highest category of Table 1) corresponds to 150–1500 μ Svy⁻¹, whereas 20 Bqm⁻³ (the mean in

the lowest category of Table 1) corresponds to 10–100 μ Svy⁻¹. If one assumes an excess risk coefficient for ALL incidence in children of 0.0006/Sv (42) and an ALL incidence rate in children of 0.00003 (43), the risk for 5-year residence in a home at 300 Bqm⁻³ relative to 20 Bqm⁻³ ranges from $(0.00003 + 0.0006 \times 150 \mu\text{Svy}^{-1} \times 5 \text{ years}) / (0.00003 + 0.0006 \times 100 \mu\text{Svy}^{-1} \times 5 \text{ years}) = 1.01\text{--}1.14$, although this range may be an overestimation due to a possible linear-quadratic dose-response effect for ALL (42). Based on a log-linear RR model with continuous radon level, the RR in our study for 300 Bqm⁻³ relative to 20 Bqm⁻³ was 0.71 (95% CI = 0.42–1.21). Thus, while the dosimetry-based estimates of RR are small and are based on uncertain extrapolations from much higher dose data, they are within the plausible range of our results.

For children under age 2 years, risk decreased (nonsignificantly) with increasing TWA radon concentration (Table 2). The reason for this decline in risk is unknown, but it could reflect chance. However, a similar pattern was observed in a case-control study of childhood acute myeloid leukemia drawn from the same target population; this study was recently carried out by the CCG in collaboration with the National Institute of Environmental Health Sciences (Steinbuch M: personal communication).

Our study has several limitations (23). Misspecification of exposure generally reduces the strength of an association with disease (44), and a 1-year measurement in one or two rooms in current and past homes may not characterize precisely radon progeny dose to target cells. We defined the relevant exposure period as 5 years prior to case incidence. Analyses of populations exposed to γ rays and x rays indicate that this period should include disease-relevant exposures (45), although it is unknown whether this time period is appropriate for α radiation from radon progeny. In our study, 79% of children with reference age of 10 years or greater lived in one house (mean length of residence, 8.4 years). There was no indication of an increased risk of ALL (Table 2). Thus, if an association exists, then the minimal latency interval for residential radon exposure would have to be in excess of 8 years. Results from studies of patients given an injection of Thorotrast (thorium dioxide, an α emitter used as a angiographic contrast medium) are not directly relevant, since children were generally not given an injection. In adults, the predominant leukemia subsequent to Thorotrast injection was acute myeloid leukemia; the minimum latent period was 5 years (46).

Our study has several notable strengths (22,23). Data for subjects were collected by direct interviews of parents, and homes were measured within a short period from time after enrollment. Leukemia incidence was evaluated, which is preferred over a mortality analysis. Residential stability was part of the measurement protocol, and coverage of the exposure assessment period by radon measurements was nearly complete for all subjects. Extensive information on a wide range of potentially confounding variables was obtained for each child and evaluated. Finally, the size of our study—281 ALL case subjects in the matched analysis and 505 ALL case subjects in the unmatched analysis—far exceeded the 15 case subjects with childhood cancer in the only other study of this issue reported to date (16).

In summary, geographic correlation studies raised the pro-

vocative hypothesis that indoor radon exposure might potentially be responsible for a substantial proportion of childhood leukemias. Our study found no association between indoor radon exposure and ALL, overall or in various subgroups, and thus offers no support for the hypothesis of such an association.

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